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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/533,547 | 03/23/2000 | Randall S. Kent | JAO 28796.02 | 3851 |

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| EXAMINER | |
|---|---|
| MCKANE, ELIZABETH L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1744 | |

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/533,547 | KENT ET AL. | |
| | Examiner | Art Unit | |
| | Leigh McKane | 1744 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 July 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *197-243* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *197-243* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 197-201, 203-211, 215-217, 219-221, 230, 234, 235, and 238-243 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson (U.S. Patent No. 5,730,933).

Peterson teaches the use gamma radiation to sterilize a biological material (e.g. skin, cartilage, tendon, plasma, serum, albumins, globulins, proteins, demineralized bone matrix, growth factors, etc.) that is sensitive to radiation, wherein a stabilizer (antioxidant/free-radical scavenger, such as ascorbate or butylated hydroxytoluene) in combination with an extraneous protein (also a stabilizer) is added to the material prior to irradiation and the material is then irradiated within a package "under standard sterilization conditions...at an intensity and for a time duration sufficient to destroy substantially all of the microorganism contamination" (col.4, lines 59-64). See also col.3, lines 35-65; col.4, lines 36-51; col.6, lines 1-18. The material may also be lyophilized or dried with drying agents and/or frozen and placed under a vacuum or inert gas, such as nitrogen or argon (col.4, lines 51-58; col.5, lines 28-35 and lines 53-67). The biological material may be a protein created by recombinant methods. See col.3, lines 45-46.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 202 and 223-226 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson.

With respect to claim 202, Peterson fails to expressly teach sterilization of a combination of hard and soft tissue. However, since Peterson does disclose the sterilization of both soft and hard tissues, it is deemed obvious to one of ordinary skill in the art to sterilization a combination of both hard and soft tissue when the biological material is present in a combination.

As to claim 223, Peterson teaches applying a dose of "about 1 to about 3 mRad" (10-30 kGy). However, Peterson also discloses that the conditions of sterilization are those which at an intensity and a time sufficient "to destroy substantially all of the microorganism contamination". See col.4, lines 59-64. Therefore, it would have been obvious to increase the total dose as necessary to achieve adequate sterilization.

With respect to claims 224-226, Peterson discloses using the stabilizer in a concentration of about 0.01 to about 10 weight percent (col.4, line 47). Regardless, one of ordinary skill in the art would have found it obvious to optimize the concentration of the stabilizer as being a result effective variable.

5. Claims 212-214, 228, 233, 236, and 237 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Horowitz et al (U.S. Patent No. 5,981,163).

With respect to claims 212-214, Peterson teaches the sterilization of proteins such as globulins, hormones, growth factors, and blood products, but does not disclose the sterilization of clotting factors or immunoglobulins. Horowitz et al discloses that clotting factors such as Factor XIII and fibrinogen, and immunoglobulins such as immunoglobulins G, M, A, and E can all be sterilized using a combination of radiation ($\gamma$) and a stabilizer. See col. 5, lines 60-68. Thus, it would have been obvious to use the method of Peterson to also sterilize clotting factors and immunoglobulins as one would have had an expectation of success in doing so.

As to claim 228, Peterson teaches the use of stabilizers but fails to teach the use of mannitol as a stabilizer. Horowitz et al discloses the use of an irradiation stabilizer, selected from polyhydric alcohols (such as mannitol), rutin, glutathione, and others. See col.7, lines 1-7. As Horowitz et al teaches their use in the sterilization of sensitive biological materials with gamma radiation and discloses that these stabilizers are effective in reacting with both free radicals and reactive forms of oxygen, it would have been obvious to use the stabilizer of Horowitz et al in the method of Peterson, especially as Peterson teaches that other antioxidants are acceptable.

With respect to claim 233, Peterson fails to disclose adding a sensitizer to the biological material before irradiation. Horowitz et al teaches sterilizing biological material wherein a sensitizer may be added before irradiation. See col.6, line 64 to col.7, line 10. Horowitz et al disclose that the use of a sensitizer achieves preferential damage to the virus, but not to the

biological material. For this reason, it would have been obvious to add a sensitizer in the method of Peterson.

As to claims 236 and 237, Peterson teaches lyophilization of the product, but does not teach that the solvent removed is an organic solvent. Horowitz et al, however, teaches that it is known in the art to combine a radiation sterilization step with another sterilization step such as treatment with an organic solvent. See col.7, line 66 to col.8, line 7. Since it would have been obvious to first treat the product with a solvent to inactivate viruses, it would have been further obvious to remove the solvent before irradiation.

6. Claim 218 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Zabal et al (abstract of "Contamination of fetal bovine serum with bovine viral diarrhea virus").

Peterson teaches the sterilization of serum but does not specficially teach the sterilization of FBS. Zabal et al discloses that it was known in the art at the time of the invention to employ gamma radiation for the sterilization of FBS. Thus, it would have been obvious to use the method of Peterson for the sterilization of FBS.

7. Claim 222 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Chanderkar et al ("The Involvement of Aromatic Amino Acids in Biological Activity of Bovine Fibrinogen as Assessed by Gamma-Irradiation").

Peterson does not disclose a rate at which to apply the gamma radiation. Chanderkar et al teaches sterilization of fibrinogen in lyophilized form in the presence of an electron scavenger (potassium iodide). The preparation is irradiated by gamma radiation with a dose rate of 12,500 R/min (7.5 kGy/hr). See pages 283-284. As the conditions and biological material are similar to

those of Peterson, it would have been obvious to use the irradiation rate of Chanderkar et al in the method of Peterson.

8. Claim 227 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Freistedt et al (Abstract of DD 280466).

With respect to claim 227, Peterson discloses the use of stabilizers in a method of gamma radiation sterilization but fails to teach DMSO as the stabilizer. Freistedt et al teaches a method of tissue sterilization wherein a stabilizer(s) such as DMSO is added to the tissue prior to irradiation. As Freistedt evidences that DMSO is an effective stabilizer for tissue sterilization, it would have been obvious to use in the method of Peterson.

9. Claim 229 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Okrongly et al (U.S. Patent No. 5,283,034).

Peterson discloses the use of stabilizers in a method of gamma radiation sterilization but fails to teach DMSO as the stabilizer. Okrongly discloses that it was known in the art at the time of the invention to add radioprotectants such as polyols or reduced forms thereof to surfaces undergoing radiation sterilization for the purpose of oxygen scavenging. Particularly disclosed are mannitol and trehalose. It would have been obvious to use trehalose as the stabilizer in the method of Peterson as Peterson indicates that the invention is not limited to the disclosed stabilizers.

10. Claims 231 and 232 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Freistedt et al and Horowitz et al.

Peterson teaches the use of two stabilizers (an extraneous protein in combination with a free-radical scavenger), but fails to teach the combined use of DMSO and mannitol. Freistedt et

al teaches the combined use of DMSO and a polyol (propylene glycol) as radioprotectants during tissue irradiation sterilization. Horowitz et al teaches a method of radiation sterilizing sensitive biological materials combined with stabilizer mixtures. The stabilizer/scavenger can be mannitol and/or glycerol, among others.

One of ordinary skill in the art would have found it obvious to use the stabilizer mixture of Freistedt et al in the method of Peterson, as being effective in protecting sensitive tissues during radiation. Moreover, it would have been obvious to substitute one polyol stabilizer for another where the results are not unexpected.

## *Conclusion*

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh McKane whose telephone number is 571-272-1275. The examiner can normally be reached on Monday-Wednesday (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert J. Warden can be reached on 571-272-1275. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leigh McKane

**Leigh McKane**
**Primary Examiner**
**Art Unit 1744**

elm
1 September 2004